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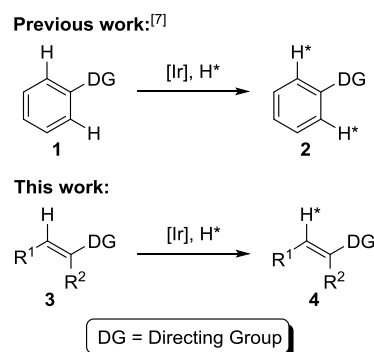
Iridium(I)-catalyzed Regioselective C-H Activation and Hydrogen Isotope Exchange of Non-aromatic Unsaturated Functionality**

William J. Kerr,^{*,[a]} Richard J. Mudd,^[a] Laura C. Paterson,^[a] and Jack A. Brown^[b]

Abstract: Isotopic labeling is a key technology of increasing importance for the investigation of new C-H activation and functionalization techniques, as well as in the construction of labeled molecules for use within both organic synthesis and drug discovery. Herein, we report, for the first time, selective iridium-catalyzed C-H activation and hydrogen isotope exchange at the β -position of unsaturated organic compounds. The use of our highly active $[\text{Ir}(\text{COD})(\text{IMes})(\text{PPh}_3)]\text{PF}_6$ catalyst, under mild reaction conditions, allows the regioselective β -activation and labeling of a range of α,β -unsaturated compounds with differing steric and electronic properties. This novel process delivers high levels of isotope incorporation over short reaction times, using low levels of catalyst loading.

The functionalization of *aromatic* C-H bonds *via* transition metal-mediated C-H activation has been widely developed in the past several decades, delivering key compounds for use in an array of chemical domains.^[1] In contrast, regioselective activation of *olefinic* C-H bonds has received much less attention, with the majority of studies to date focussed upon the application of homogeneous organometallic complexes of ruthenium^[2] and rhodium.^[3] Indeed, very little knowledge exists surrounding the use of iridium-based complexes in this area,^[4] despite their widespread activity in aromatic C-H bond activation.^[1a,b,h,k,o] In relation to this, transition metal-mediated hydrogen isotope exchange (HIE) is a technique of increasing importance, often being used as a first step in creating new C-H activation methods and as a means to generate deuterated feed stocks for mechanistic studies.^[5] Furthermore and importantly for medicinal chemists, such direct and flexible labeling processes now represent a central tool for fast and efficient incorporation of a tracer into drug candidates, enabling various metabolic, stability, and toxicity studies to be performed earlier in the drug design process.^[5a,6] Recent studies from our own laboratory^[7] have disclosed a series of highly active iridium(I) catalysts of the type $[\text{Ir}(\text{COD})(\text{IMes})(\text{PR}_3)]\text{X}$ capable of delivering heavy isotopes of hydrogen (deuterium and tritium) to aromatic molecules *via* an *ortho*-directed C-H insertion process under mild conditions

(Scheme 1). Indeed, our developed methods have enabled access to a broad spectrum of labeled new chemical entities of direct relevance to pharmaceutical partners and have provided a platform for on-going C-H activation endeavors. Expanding on our initial developments, we now report the first example of selective C-H activation and hydrogen isotope exchange at the β -position of a range of α,β -unsaturated moieties, extending the applicability of our emerging catalyst series and addressing the requirement for mild and selective means of accessing labeled olefinic substrates.^[8]



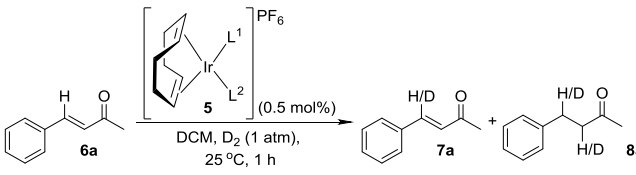
Scheme 1. Previous and proposed labeling procedure.

Our initial studies involved the application of conditions developed in our laboratory for the isotopic labeling of aromatic substrates.^[7a] As such, (*E*)-4-phenylbutenone, **6a**, was treated with just 0.5 mol% of our iridium catalyst series (**5a-c**) in DCM and exposed to 1 atm. of D_2 gas (Table 1, Entries 1-3).^[9] As expected, and based on the differing steric properties of our series of catalysts, varying results were obtained. Catalyst **5a**, bearing the smallest (PMe_2Ph) phosphine ligand, produced solely the reduced product **8a** with quantitative conversion (Entry 1), with this result being somewhat expected due to our recent disclosure that such iridium complexes can act as extremely efficient hydrogenation catalysts.^[10] Catalyst **5b**, containing the bulky yet flexible tribenzylphosphine ligand, showed high levels of deuterium incorporation, albeit with **8a** remaining as the major product (Entry 2). Pleasingly, a switch in selectivity was observed when moving to the most rigid of our catalyst range (**5c**), whereby the high level of deuterium incorporation was maintained and appreciable selectivity for the desired labeled compound was achieved (Entry 3). Until recently, Crabtree's catalyst, **5d**,^[11] was the most widely adopted species in the domain of iridium-catalyzed, *ortho*-directed HIE in aromatic compounds, despite the regular necessity for stoichiometric loadings.^[12] In this study, Crabtree's catalyst (**5d**) displayed a similar level of deuterium incorporation to **5c**, however, with virtually no selectivity for HIE versus reduction (Entry 4). On

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GlaxoSmithKline is gratefully acknowledged. Mass spectrometry
data were acquired at the EPSRC UK National Mass Spectrometry
Facility at Swansea University.

Supporting information for this article is given via a link at the end of
the document.

Table 1. Screening of catalysts **5a-d** for HIE of **6a**.^[a]


Entry	L ¹ , L ²	Complex	%D Incorporation in 7a ^[b]	7a:8a ^[b]
1	IMes, P(Me) ₂ Ph	5a	0%	0:100
2	IMes, PBN ₃	5b	86%	6:94
3	IMes, PPh ₃	5c	95%	77:23
4	Py, PCy ₃	5d	96%	46:54
5 ^[c]	IMes, PPh ₃	5c	88%	94:6
6 ^[d]	IMes, PPh ₃	5c	78%	99:1

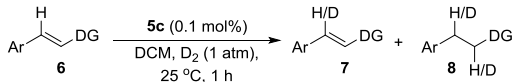
[a] Each entry displays the average of two reaction runs. [b] Calculated from the NMR spectra of crude reaction material. [c] **6a** (0.4 mmol), DCM (8 mL), **5c** (0.1 mol%). [d] **6a** (0.4 mmol), DCM (1 mL), **5c** (0.1 mol%).

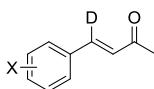
further optimization of the reaction conditions using catalyst **5c**, we were delighted to observe that a reduction in catalyst loading to 0.1 mol% resulted in an excellent selectivity of 94:6 for the desired β-labeled enone product, **7a**, whilst maintaining high D incorporation levels (Entry 5). Furthermore, increasing the concentration of the reaction delivered **7a** almost exclusively with 78% D labeling (Entry 6).

With conditions in hand that produce appreciable selectivity for β-C-H activation and hydrogen isotope exchange, we looked to further explore the capabilities of our developed system by extending the substrate scope (Table 2). In this regard, our initial focus was directed towards the manipulation of the chemical properties of the arene component present in **6**. We were pleased to find that substituents of varying electronic properties were tolerated well at the 4-position of the arene substrate, with high levels of deuterium incorporation and very good selectivities being achieved using just 0.1 mol% catalyst loading in all cases (**7b-g**). Further to this, steric encumbrance adjacent to the labeling position was investigated as in **6h** and **6i**. Encouragingly, *meta*-substituted compound **6h** did not hinder appreciably the HIE process, however, a drop in deuterium incorporation was observed upon labeling *ortho*-substituted analogue **6i**, presumably due to an unfavorable steric interaction between the catalyst and the *ortho*-substituted aryl ring, affecting the key C-H activation process. On the other hand, the pharmaceutically-relevant thiophene derivative **6j** displayed high incorporation and excellent selectivity. Our studies continued with investigations into the nature of the directing group. Notably, good incorporation levels were observed in compounds **7k-m** albeit with slightly diminished selectivity between HIE and

reduction for **7k** and **7l**. Presumably this can be attributed to the nature of the intermediate formed upon directing group coordination and the reversibility of this process; as well as facilitating faster decomplexation, we envisage that the larger substrates will adopt a less planar conformation upon binding to the catalyst, potentially better suited towards the reduction pathway. Having stated this, selectivity was restored in **7k** following employment of an even lower level of catalyst loading (0.025 mol%), highlighting the level of activity presented by catalyst species **5c** for this labeling process. Finally, we were also pleased to discover that alternative directing groups such as amide or nitro functionalities facilitated the regioselective C-H activation and exchange process with appreciable efficiency (**6n-o**). Indeed, substrate **6o** represents, to the best of our knowledge, the first example of a nitro moiety directing such a β-C-H activation.

Table 2. Substrate scope with Ir catalyst **5c**.^[a]





X = **7a** H 78% (99:1)

7b 4-CF₃ 89% (98:2)

7c 4-Ph 82% (98:2)

7d 4-Cl 90% (97:3)

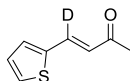
7e 4-Br 87% (98:2)

7f 4-Me 70% (99:1)

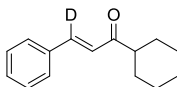
7g 4-OMe 81% (99:1)

7h 3-OMe 75% (99:1)

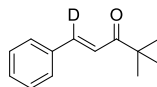
7i 2-OMe 44% (98:2)



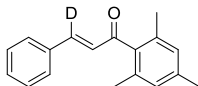
7j 84% (99:1)



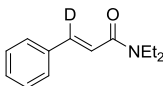
7k 98% (70:30)
92% (93:7)^[b]



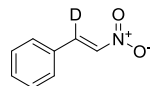
7l 93% (87:13)



7m 88% (99:1)



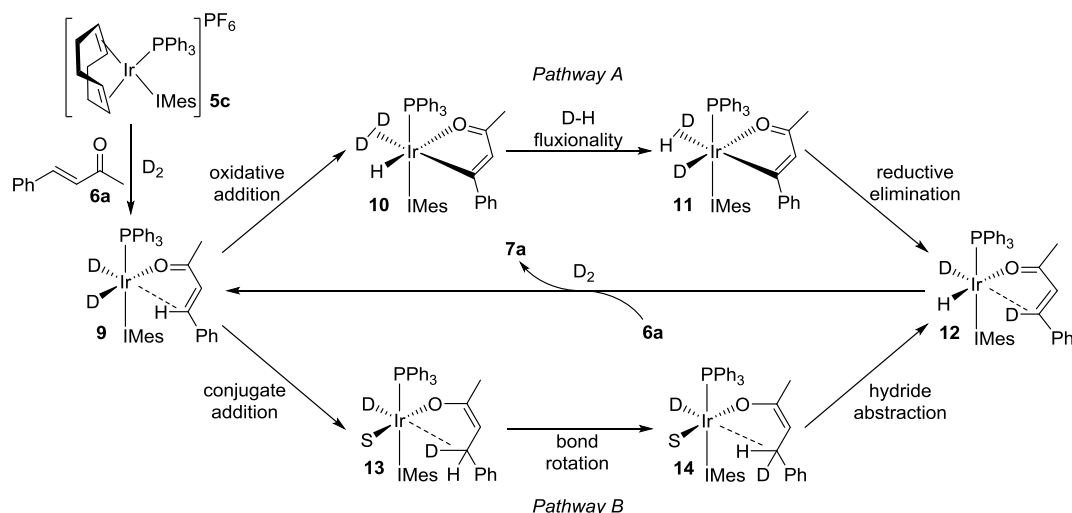
7n 84% (96:4)^[c]



7o 83% (95:5)

[a] Each entry displays the average of two reaction runs and the results presented as %D incorporation in **7** with the selectivity of **7:8** shown in parentheses. [b] 0.025 mol% of **5c** was employed. [c] 0.25 mol% of **5c** was employed.

In relation to the reaction mechanism, and based on Heys' original proposal in 1996,^[13] we have recently disclosed experimental and computational studies which have led to escalated insight into the possible sequence of events that our 'ortho'-directed HIE process follows.^[7d] In this regard, a similar process could be envisaged for the olefinic substrates described within this contribution (Pathway A, Scheme 2). Following catalyst activation with D₂, coordination of the substrate, e.g. **6a**, delivers intermediate **9**, where the β-H atom is associated with the iridium center *via* an agostic interaction, consistent with our related *ortho* aryl labelling mechanistic studies.^[7d] Subsequent oxidative addition delivers **10**, followed by hydride fluxionality bringing isotopic hydrogen *cis* to the activated complex as in **11**. Finally, reductive elimination and decomplexation releases the labeled product **7a** and regenerates **9** under the deuterium

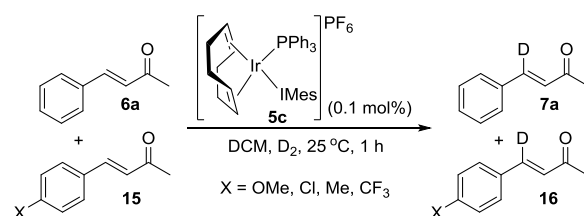


Scheme 2. Possible HIE mechanistic pathways; all intermediates within this process are assumed to be cationic, with the counter being omitted for clarity.

atmosphere. In contrast, one could also consider that the β -selective labeling process proceeds in the manner described by Pathway B, Scheme 2. In this case, following the same catalyst activation sequence to generate **9**, the intramolecular delivery of a deuteride in a conjugate manner would provide enolate-type intermediate **13** (where S = solvent). Following bond rotation to give **14**, the cycle is completed with hydride abstraction and decomplexation.

To probe these mechanistic proposals, we conducted a series of additional experimental studies. Firstly, Hammett studies were employed, whereby competition reactions were run for the HIE of substrate **6a** versus a selected set of four *p*-substituted enone substrates (**15**, Scheme 3). Following ¹H NMR analysis and construction of the Hammett plot, a relatively small negative slope of -0.64 was revealed, indicating that whilst electron-donating functionality facilitates an increase in HIE, such influence does not occur during the rate determining step of the reaction (see Supporting Information for full details).^[14] This electronic effect can be envisaged as being a result of the increased binding ability of the more electron-rich substrates with the iridium catalyst; this effect would be observed within both pathways A and B. Having stated this, the magnitude of the Hammett ρ value indicates that no significant build-up of charge is evident during the rate-limiting step of the overall process and, as such, this lends some support to mechanistic pathway A, i.e. via insertion intermediate **10** as opposed to the enolate-type structure **13** proposed in pathway B. Further, it is important to note that both the (*Z*)-isomer of substrate **6a** and cyclohexenone fail to label under the developed protocols; we believe that both of these latter substrates would be unable to undergo the insertion process proposed within mechanistic pathway A (see Supporting Information for full experimental details).

In relation to these preliminary mechanistic investigations, further analysis attempted to strengthen our proposals by measuring the kinetic isotope effect (KIE) within our developed



Scheme 3. Competition studies for the HIE of **6a** versus *p*-substituted enone substrates.

HIE process. Monitoring the rate of our standard reaction, as well as the reverse process (employing H₂ in place of D₂ with fully deuterated **7a**), revealed a primary KIE value of 3.8, thus strongly indicating that C-H activation is involved in the rate-limiting step, and in line with pathway A. Indeed, if pathway B were to be favoured, one would expect an inverse KIE value if conjugate addition was rate determining, or a much larger KIE value (≥ 5) for hydride abstraction.^[15] Notably, the stoichiometric isolation of intermediates similar to **10** by Crabtree further supports this proposed pathway A.^[4c]

In summary, we have established the first β -selective iridium-catalyzed C-H activation and hydrogen isotope exchange process using our active iridium(I) catalyst, [Ir(COD)(IMes)(PPh₃)]PF₆. Under practically accessible reaction conditions, and employing low levels of catalyst loading, very good levels of deuterium incorporation have been obtained with appreciable selectivity over the potentially competing reduction process across a series of α,β -unsaturated substrates. Additional experimental studies have enhanced our insight into the possible mechanistic pathway being followed, whereby it is believed that a C-H activation process is the rate-limiting step of the overall transformation. Our work continues within this area to fully elucidate the mechanism of these emerging transformations and seeks to further understand the origins of our observed

selectivity, with the overall aim of applying our developing techniques to a wider array of C-H activation processes.

Keywords: C-H activation • iridium • hydrogen isotope exchange • unsaturated compounds • deuterium

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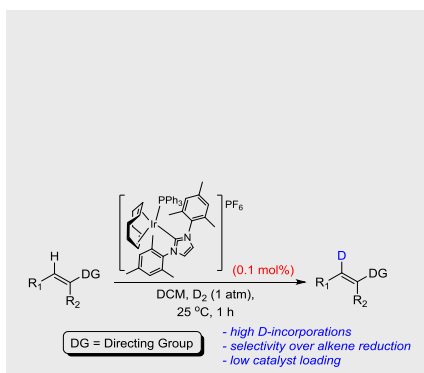
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Layout 1:

COMMUNICATION

***β*-Selective activation with iridium:**

Efficient and selective olefinic C-H activation and D labeling is achieved by mild iridium catalysis (see scheme).



Prof. Dr. William J. Kerr,* Richard J. Mudd, Dr. Laura C. Paterson, and Dr. Jack A. Brown

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Iridium(I)-catalyzed Regioselective C-H Activation and Hydrogen Isotope Exchange of Non-aromatic Unsaturated Functionality